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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/373,403	08/12/1999	WILLIAM R. ARATHOON	P1099C1	2534

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/373,403	ARATHOON ET AL.	
	Examiner	Art Unit	
	ANNE L. HOLLERAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11/20/2007 has been entered.

The indicated allowability of the claims is hereby WITHDRAWN upon further consideration.

Claims 56-77 are pending and examined on the merits.

Information Disclosure Statement

The references cited in the IDS filed 11/20/2007 have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 67-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 67 is indefinite because section (i) appears to contradict the description of the polypeptides set forth in subsection (b). Section (i) is a selecting step where at least three nucleic acids are selected, a nucleic acid encoding a first polypeptide, a nucleic acid encoding a light chain and at least one additional nucleic acid encoding at least one additional polypeptide, whereas, subsection (b) describes a first polypeptide and an at least one additional polypeptide as each comprising a binding domain that comprises a heavy chain variable domain and a light chain variable domain. Thus, there does not need to be a nucleic acid encoding a light chain, if the nucleic acid encoding a first polypeptide that comprises a light chain variable domain.

Claims 68 and 69 are indefinite because "the altering" lacks antecedent basis in claim 67, from which both claims depend.

Claims 71 and 72 are indefinite because "the antibody constant domain" lacks antecedent basis in claim 67, which recites a heavy chain constant domain. The "antibody constant domain" encompasses a structure from a whole antibody that includes the constant regions from both the heavy and light chains.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 77 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 77 introduces new matter into the specification as originally filed. Claim 77 is drawn to a method of claim 76, which is a method wherein the multimerization domain of the first polypeptide has a protuberance and the mulitimerization domain of the at least one additional polypeptide has a cavity, where claim 77 adds the limitation that the multimerization further comprises a non-naturally occurring disulfide bond. Thus, claim 77 is drawn to a method for making multispecific antibodies having a multimerization domain with a protuberance and cavity interaction in addition to a disulfide bond. The amendment which originally introduced a claim of this nature was filed 5/13/2004. The passages pointed to by applicant in the remarks accompanying the amendment do not provide support for a method encompassed by claim 77. Furthermore, an examination of the specification does not reveal any support for subject matter of claim 77. Therefore, it does not appear that the inventors were in possession of the invention of claim 77 at the time the application was filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 56, 58-68, 70, 71 and 73-76 are rejected under 35 U.S.C. 103(a) as being obvious over Carter-A (US 5,731,168 issued Mar. 24, 1998; effective filing date is March 1, 1995; cited in a previous Office action 11/02) in view of de Kruif-A (de Kruif, J. et al. The Journal of Biological Chemistry, 271 (13): 7630-7634, 1996; cited in IDS) and further in view of de Kruif-B (de Kruif, J. et al, J. Mol. Biol., 248: 97-105, 1995; cited in IDS).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the

inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Carter-A teaches methods of making bispecific antibodies comprising culturing a host cell comprising a nucleic acid encoding a first polypeptide and nucleic acid encoding at least one additional polypeptide, wherein the first polypeptide and the at least one additional polypeptide comprise multimerization domains that contain a heavy chain constant domain forming an interface positioned to interact with an interface of the multimerization domain of the at least one additional polypeptide (column 5, line 34- column 6, line 47; see claims 1-18, 21-28 and 31-41). These polypeptides also form binding domains that comprise scFv antibody fragments (column 9, lines 47-62 and column 17, lines 36 – 53), with one binding domain having one specificity and the other binding domain having a second, different specificity (column 10, lines 25-30). The interaction between the multimerization domains comprise a protuberance-into-cavity interaction, which is generated by altering the first polypeptide by substituting an amino acid of the first polypeptide with an amino acid that has a larger side chain volume than the substituted amino acid and the cavity is generated by altering the at least one additional polypeptide by

substituting an amino acid of the at least one additional polypeptide with an amino acid that has a smaller side chain volume than the substituted amino acid (column 11, line 62 – column 14, line 38). Carter-A teaches the specific residues for substitution that are listed in instant claims 61 and 62 (see claims 4-13, columns 52-53; and column 12, lines 59 – column 13, line 26). Carter-A teaches methods for making bispecific antibodies comprising heavy chain constant domains that are either C_H3 domains or IgG heavy chain constant domains (column 8, line 61 - column 9, line 45). Carter-A teaches and claims host cells comprising nucleic acids encoding bispecific antibodies (column 6, lines 15-23 and claims 36-38). Carter-A teaches a selecting step as part of a method for making bispecific antibodies (see column 15, lines 25-37). Carter-A teaches use of phage display selection in the method of generating a protuberance or cavity (see column 37, line 34 – column 38, line 35).

Carter-A fails to specifically teach that the light chain variable domain for one binding domain formed by the first polypeptide will have the same amino acid sequence as the light chain variable domain for other binding domain formed by the at least one other polypeptide.

However, de Kruif-A teaches methods for making bispecific antibodies from semi-synthetic antibody phage display libraries, such as the libraries of Hoogenboom and Winter (1992), Nissim(1994) or of de Kruif (1995) (see page 7632, 2nd column). de Kruif-B teaches that libraries such as that of Hoogenboom and Winter(1992) or Nissim(1994) are libraries with collections of V_H genes combined with one light chain (see page 98, column 1, first full paragraph).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Carter-A with those of de Kruif-

A and de Kruif-B to make the claimed inventions because Carter-A teaches that bispecific antibodies may be made using methods of forming interfaces to promote heterodimerization of two different polypeptides, and because Carter-A teaches that nucleic acids encoding such polypeptides may be derived from known phage libraries. Because de Kruif-A and de Kruif-B show that antibody phage libraries containing multiple heavy chains paired with the same light chain were known in the art and useful for isolating scFv fragments that bound to different antigens, it is clear that the prior art provided antibody phage libraries that encode binding domains that are the same as those of the claimed multispecific antibodies where the sequence of the light chain is the same for each binding domain. While there is no explicit suggestion in Carter-A to choose one of the libraries provided by de Kruif-A and de Kruif-B, it would have been obvious to try to use the methods of Carter-A, which suggested the use of phage libraries as a source of nucleic acid sequences to encode the binding domains of the first and second polypeptides, with the phage libraries taught by de Kruif-A and de Kruif-B, especially since de Kruif-A suggests that bispecific antibodies may be made from such antibody phage libraries.

Claims 56, 58-68, 70, 71 and 73-76 are rejected under 35 U.S.C. 103(a) as being obvious over Carter-B (WO 96/27011; published 6 Sep., 1996; cited in IDS) in view of de Kruif-A (de Kruif, J. et al. The Journal of Biological Chemistry, 271 (13): 7630-7634, 1996; cited in IDS) and further in view of de Kruif-B (de Kruif, J. et al, J. Mol. Biol., 248: 97-105, 1995; cited in IDS).

Carter-B teaches methods of making bispecific antibodies comprising culturing a host cell comprising a nucleic acid encoding a first polypeptide and nucleic acid encoding at least one

additional polypeptide, wherein the first polypeptide and the at least one additional polypeptide comprise multimerization domains that contain a heavy chain constant domain forming an interface positioned to interact with an interface of the multimerization domain of the at least one additional polypeptide (page 6, lines 14-44; page 7, lines 10-36). These polypeptides also form binding domains that comprise scFv antibody fragments (page 10, lines 16-25 and lines 37-46; page 11, lines 17-24; and page 19, lines 2-7; page 21, lines 3-17), with one binding domain having one specificity and the other binding domain having a second, different specificity (page 1, lines 11-12; page 4, lines 8-21). The interaction between the multimerization domains comprise a protuberance-into-cavity interaction, which is generated by altering the first polypeptide by substituting an amino acid of the first polypeptide with an amino acid that has a larger side chain volume than the substituted amino acid and the cavity is generated by altering the at least one additional polypeptide by substituting an amino acid of the at least one additional polypeptide with an amino acid that has a smaller side chain volume than the substituted amino acid (page 13, line 39 – page 17, line 20). Carter-B teaches the specific residues for substitution that are listed in instant claims 61 and 62 (page 14, line 23 – page 16, line 2). Carter-B teaches methods for making bispecific antibodies comprising heavy chain constant domains that are either C_H3 domains or IgG heavy chain constant domains (page 10, lines 22-27 and page 10, line 42 - page 11, line 2). Carter-B teaches host cells comprising nucleic acids encoding bispecific antibodies (page 7, lines 10-16). Carter-B teaches a selecting step as part of a method for making bispecific antibodies (page 18, lines 19-22). Carter-B teaches use of phage display selection in the method of generating a protuberance or cavity (see page 44, line 33 - page 46, line 40).

Carter-B fails to specifically teach that the light chain variable domain for one binding domain formed by the first polypeptide will have the same amino acid sequence as the light chain variable domain for other binding domain formed by the at least one other polypeptide.

However, de Kruif-A teaches methods for making bispecific antibodies from semi-synthetic antibody phage display libraries, such as the libraries of Hoogenboom and Winter (1992), Nissim(1994) or of de Kruif (1995) (see page 7632, 2nd column). de Kruif-B teaches that libraries such as that of Hoogenboom and Winter(1992) or Nissim(1994) are libraries with collections of V_H genes combined with one light chain (see page 98, column 1, first full paragraph).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Carter-B with those of de Kruif-A and de Kruif-B to make the claimed inventions because Carter-B teaches that bispecific antibodies may be made using methods of forming interfaces to promote heterodimerization of two different polypeptides, and because Carter-B teaches that nucleic acids encoding such polypeptides may be derived from known phage libraries. Because de Kruif-A and de Kruif-B show that antibody phage libraries containing multiple heavy chains paired with the same light chain were known in the art and useful for isolating scFv fragments that bound to different antigens, it is clear that the prior art provided antibody phage libraries that encode binding domains that are the same as those of the claimed multispecific antibodies where the sequence of the light chain is the same for each binding domain. While there is no explicit suggestion in Carter-B to choose one of the libraries provided by de Kruif-A and de Kruif-B, it would have been obvious to try to use the methods of Carter-B, which suggested the use of phage libraries as

a source of nucleic acid sequences to encode the binding domains of the first and second polypeptides, with the phage libraries taught by de Kruif-A and de Kruif-B, especially since de Kruif-A suggests that bispecific antibodies may be made from such antibody phage libraries.

Claims 56, 57, 67 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu (Hu, S.-z., et al., Cancer Research, 56: 3053-3061, 1996) in view of de Kruif-A (supra) and further in view of de Kruif-B (supra).

The claims encompass methods for making bispecific antibodies comprising multimerization domains that are made up of a domain from a constant region of an antibody and also a non-naturally occurring disulfide bond, where the antigen binding domains are made of scFv fragments, where one scFv binds one antigen and the other scFv binds a second antigen.

Hu teaches that scFv dimers may be formed by ligating a nucleic acid sequence encoding an scFv domain to a nucleic acid sequence encoding a C_H3 domain with a nucleic acid sequence in between the scFv domain and the C_H3 domain, where the linker sequence encoded a hinge and Gly-Ser sequence, which included two potential disulfide bridges.

Hu fails to teach that the two scFv bind to different antigens (bispecicity). Although the light chains of Hu's scFv domains are the same for each scFv domain this is because the two scFv domains bind to the same antigen.

However, de Kruif-A teaches methods for making bispecific antibodies from semi-synthetic antibody phage display libraries encoding scFv domains, such as the libraries of Hoogenboom and Winter (1992), Nissim(1994) or of de Kruif (1995) (see page 7632, 2nd column). de Kruif-B teaches that libraries such as that of Hoogenboom and Winter(1992) or

Nissim(1994) are libraries with collections of V_H genes combined with one light chain (see page 98, column 1, first full paragraph).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Hu with those of de Kruif-A and de Kruif-B to make the claimed inventions because Hu teaches that scFv dimers may be made using methods of forming interfaces to promote heterodimerization of two different polypeptides. Because de Kruif-A and de Kruif-B show that antibody phage libraries containing multiple heavy chains paired with the same light chain were known in the art and useful for isolating scFv fragments that bound to different antigens and that scFv libraries are useful for finding scFv domains for a bispecific antibody, it is clear that the prior art provided antibody phage libraries that encode binding domains that are the same as those of the recited multispecific antibodies where the sequence of the light chain is the same for each binding domain. While there is no explicit suggestion in Hu to make bispecific scFv dimers or to choose one of the libraries provided by de Kruif-A and de Kruif-B, it would have been obvious to try to combine the methods of Hu, which teaches a method for making an scFv dimer, with the methods of using phage libraries as taught by de Kruif-A and de Kruif-B, to make bispecific scFv dimers as suggested by de Kruif-A.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
March 14, 2008

/Alana M. Harris, Ph.D./
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